Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3-9 and 11 are pending in the application, with claims 1 and 8 being the independent claims. Claim 8 has been amended to further clarify the subject matter of the present invention. Support for this amendment can be found in the previously presented claims 1 and 3-7. Accordingly, this change does not add any new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 8, 9 and 11 under 35 U.S.C. §102(b) as allegedly being anticipated by Chandran *et al.* (U.S. Pat. No. 6,890,957 B2, hereinafter "the '957 patent"). (Office Action, hereinafter "OA," at pages 2-5.) The Applicant has amended claim 8 so that claims 8, 9 and 11 now recite a method of administering glimepiride and metformin in a solid dosage form. In view of this amendment, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The '957 patent does not disclose a *solid formulation* comprising metformin and glimepiride in the relative ratios recited in Applicant's amended claims. To anticipate a claim, the reference must teach every element of the claim. *See MPEP § 2131, citing Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ...

claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). The '957 patent is directed to a liquid composition comprising metformin, the purpose of formulating metformin as a liquid is to more easily adjust the treatment dosage of metformin. The present invention is directed to a method of administering a solid dosage formulation comprising metformin and glimepiride in a synergistic amount. (*See* paragraphs [0014 and 0073].) The '957 patent does not disclose a solid formulation comprising a 500:2 to 500:1 ratio of metformin to glimepiride that has a greater than additive affect for reducing plasma glucose levels. Additionally, the '957 patent does not describe a specific solid formulation comprising metformin to glimepiride at a ratio of 500:1 to 500:2 as recited in claim 8. As such, Applicant respectfully asserts that the '957 patent does not teach each and every limitation recited in the presently amended claims, specifically a solid dosage form, and therefore does not anticipate the present invention.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1 and 3-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chandran *et al.* (U.S. Pat. No. 6,890,957 B2, hereinafter " the '957 patent") in view of Moeckel *et al.* (U.S. Pat. No. 5,955,106, hereinafter "the "106 patent") and further in view of Ghebre-Sellassie *et al.* (U.S. Pat. No. 6,499,984 B1), hereinafter "the 984 patent"). (OA at pages 6-8.) The Examiner asserts that the claimed pharmaceutical formulations "wherein the weight ratio of glimepiride and metformin or pharmaceutically acceptable salt thereof is about 1/500 to about 2/500, which overlaps the weight ratio range of Chanran *et al.*" (OA at page 6.) "To the extent that the weight ratios of the prior art and the instant claims overlap, the synergistic effect of the composition is construed to the an inherent feature of the composition." (OA at pages 6-

7.) The Examiner further cites the '106 patent for teaching an "improved method of preparing metformin solid dosage." (OA at page 7.) The Examiner cites the '984 patent for teaching "methods of preparing tablet forms of an antidiabetic drug, including glimepiride and metformin." (OA at page 7.) The Applicant respectfully traverses this rejection as it may apply to the presently pending claims.

The references cited by the Examiner do not disclose all of the elements of the present claims. Thus, the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984).

The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving *Graham* inquiries has recently been emphasized by the Office within its published Examination Guidelines. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc. Fed. Reg.* 72:57526- 57535 (October 10, 2007), hereinafter "Examination Guidelines." To establish a *prima facie* case of obviousness it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art (*see* Examination Guidelines at page 57529). Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination

teach all of the elements of the claims, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result.

1) The '957 patent

The '957 patent is directed to a *liquid composition* comprising metformin, the purpose of formulating metformin as a liquid is to more easily adjust the treatment dosage of metformin. The present invention is directed to a solid dosage formulation comprising metformin and glimepiride in a synergistic amount. (*See* paragraphs [0014 and 0073].) The Examiner has not established why a person of ordinary skill in the art would abandon the dosage-adjustable liquid formulation described in the '957 patent for a solid formulation as recited in the rejected claims.

There is no disclosure in the '957 patent that a metformin/glimepiride formulation demonstrates a synergistic effect at any dose combination. The '957 patent discloses a generic range of sulfonylurea to metformin at a weight ratio of 1/50 to 1/300, with the preferred range of 1/75 to 1/250. The '957 patent is silent with respect to a sulfonylurea/metformin formulation producing a synergistic effect of lowering blood glucose levels in a patient.

The '957 patent does not exemplify any sulfonylurea/metformin formulation. The '957 patent broadly discloses that any known sulfonylurea, which includes glimepiride, or any antihyperglycimic agent may be used in combination with metformin. The '957 patent discloses that the preferred sulfonylureas are glyburide and glipizide. Thus, the disclosure of the '957 patent would not direct the ordinary artisan to using glimepiride (*see* the '957 patent, col. 8 lines 1-17), especially in light of the observation that not all metformin/sulfonylurea combinations exhibit a synergistic effect. For example, a

combination of metformin with glyburide at a ratio of 75:1 does not result in a synergistic lowering of blood glucose levels in a diabetic patient. (*See* U.S. Pat. Appl. No. 6,011,049 B2, Form PTO-892 of December 5, 2006, col. 16, lines 21-35.) Illustrated in the following table is a comparison of the results observed with a combination of metformin plus glyburide with the results of the combination of the present invention:

	Metformin 500 mg (present invention)	**Glimepiride 1 mg** (present invention)	**Metformin + Glimepiride 500 mg / 1mg** (present invention)	Metformin + Glyburide[1] 1500 mg / 20 mg (U.S. Pat. No. 6,011,049)
Glycosylated Hemoglobin -HbA_{1c}	+0.06	+0.25	**-0.70**	+0.10
Fasting Plasma Glucose Levels	+0.75	+0.68	**-1.77**	+6.0

The ordinary artisan would expect that combining two components where each component individually is known to reduce blood glucose levels would result in the additive effect of both components. The ordinary artisan would also expect that if you take more of each component the effect would increase proportionally with increasing amounts of the drug. However, this is not observed with the combination of metformin plus glyburide. Metformin plus glyburide at significantly increased doses, 3x more metformin and 20x more sulfonylurea, does not have the an additive effect in lowering the glycosylated hemoglobin levels or fasting blood glucose levels, and does not possess a synergistic effect. Thus, synergy with the claimed combination, at the claimed ratios, in the present application is not predictable.

Here, the Applicant has unexpectedly discovered that the claimed solid formulations of metformin plus glimepiride in a range of 500:2 to 500:1 has a synergistic effect on reducing blood glucose levels in a diabetic patient. (*See* specification

paragraphs [0012 and 0014].) The efficacy of the combination is greater than the additive effect of each individual component, thus, the effect is synergistic. (*See* specification paragraph [0012].)

In making this obviousness rejection the Examiner fails to consider the unexpected results of the present formulation

The Examiner asserts that "[t]o the extent that the weight ratios of the prior art and the instant claims overlap, the synergistic effect of the composition is construed to the an inherent feature of the composition." (OA at page 7.) The Applicant respectfully traverses this rejection.

The Examiner is improperly making an inherent anticipation argument in the context of a 35 U.S.C. § 103(a) rejection. Not all metformin/sulfonylurea combinations exhibit a synergistic effect. As discussed above, a combination of metformin with glyburide at a ratio of 75:1 does not result in a synergistic lowering of blood glucose level in a diabetic patient. (*See* U.S. Pat. Appl. No. 6,011,049 B2, Form PTO-892 of December 5, 2006, col. 16, lines 21-35.) Thus, the '957 patent does not provide any information that would indicate that the combination of metformin plus glimepiride in the claimed ratios would predictably produce a synergistic result. The Applicant asserts that the Examiner has failed to establish a *prima facie* case of obviousness based on the reference because there is no showing in the reference that this combination of metformin plus glimepiride predictability lowers blood glucose levels in synergistic manner. Even if a *prima facie* case of obviousness has been established, which it has not, Applicant respectfully contends that the unexpected result of the synergistic

[1] Glyburide is a sulfonylurea and a preferred embodiment of the '957 patent.

lowering of blood glucose levels in a patient using the claimed composition is sufficient to overcome this rejection.

2) The '106 patent

The '106 patent does not rectify the shortcomings of the '957 patent. The '106 patent does not disclose a solid formulation comprising metformin and glimepiride. The '106 patent discloses a method of compacting metformin into a solid dosage form. The '106 patent does not describe administering a solid composition of metformin in combination with glimepiride. Furthermore, the '106 patent is silent with regard to a synergistic effect upon the administration of a solid dosage form comprising a combination of metformin and glimepiride at any ratio.

3) The '984 patent

The '984 patent does not rectify the shortcomings of the '957 patent. The '984 patent at most discloses the production of tablets that can include metformin or glimepiride. The '984 patent does not disclose a solid dosage form comprising both metformin and glimepiride in a single dosage form. The '984 patent is silent with regard to showing a synergistic effect upon the administration of a solid dosage form comprising a combination of metformin and glimepiride at any ratio.

In summary, the Examiner has not demonstrated that the combination of references would lead the ordinary artisan to predictably arrive at a synergistic composition comprising a solid dosage form of metformin and glimepiride at the claimed ratios. To sustain a rejection based on obviousness requires a showing that only knowledge which was within the level of ordinary skill at the time the claimed invention was made is used, and does not include knowledge gleaned only from the Applicant's

disclosure. *See In re McLaughlin*, 443 F.2d 1392 (CCPA 1971), and MPEP §2142. Here, the Applicant has established that the claimed solid dosage form of metformin and glimepiride in a range of 500:2 to 500:1 has a synergistic effect on reducing blood glucose levels in a diabetic patient. (*See* specification paragraphs [0012 and 0014].) It is unexpected that the efficacy of the combination of metformin plus glimepiride is greater than the additive effect of the individual components. (*See* specification paragraph [0012].)

The Examiner is reminded that in order to provide a proper basis for establishing a *prima facie* case of obviousness the results of the combination of references must be predicable. Because, not all formulations comprising metformin and a sulfonylurea produce a synergistic effect the combination of references cannot be extrapolated to arrive at the presently claimed invention without applying knowledge gleaned from Applicant's disclosure.

Applicant respectfully requests reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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